

University of Groningen

Self-rated arousal concurrent with the antidepressant response to total sleep deprivation of patients with a major depressive disorder

Burg, W. van den; Beersma, D.G.M.; Bouhuys, A.L.; Hoofdakker, R.H. van den

Published in:
Journal of Sleep Research

DOI:
[10.1111/j.1365-2869.1992.tb00042.x](https://doi.org/10.1111/j.1365-2869.1992.tb00042.x)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1992

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Burg, W. V. D., Beersma, D. G. M., Bouhuys, A. L., & Hoofdakker, R. H. V. D. (1992). Self-rated arousal concurrent with the antidepressant response to total sleep deprivation of patients with a major depressive disorder: a disinhibition hypothesis. *Journal of Sleep Research*, 1(4), 211-222.
<https://doi.org/10.1111/j.1365-2869.1992.tb00042.x>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Self-rated arousal concurrent with the antidepressant response to total sleep deprivation of patients with a major depressive disorder: a disinhibition hypothesis

W. VAN DEN BURG*, D. G. M. BEERSMA, A. L. BOUHUYS
and R. H. VAN DEN HOOFDACKER

Departments of Neuropsychology* and Biological Psychiatry, University of Groningen, The Netherlands

Accepted in revised form 20 May 1992; received 7 October 1991

SUMMARY In view of the opposing theories regarding the arousing or de-arousing action of total sleep deprivation (TSD) in producing antidepressant effects, 23 patients with a major depressive disorder were deprived of a night's sleep twice weekly for two weeks, and self-rated their condition 38 times using von Zerssen's scale for depression and, concurrently, Thayer's Activation Deactivation Adjective Check List (AD ACL). Transient relief of depression after TSD, indicated by eight patients, was mimicked by their AD ACL scores, which revealed the same underlying factors as were found in Thayer's studies. TSD appears to be simultaneously arousing (giving more energy) and de-arousing (leading to less tension), while this response takes place against a background of increased tiredness/sleepiness. It is argued that TSD sets off a psychological disinhibition process on the basis of cerebral fatigue; in particular the prefrontal (orbital?) areas of the cerebral cortex may be implicated, possibly in relation to a dampening down of subcortical arousal systems.

KEYWORDS depression, inhibition, prefrontal cortex, self-rated arousal, simultaneous components analysis, sleep deprivation

INTRODUCTION

Since the pioneering studies by Pflug and Tölle (1971; Pflug 1976) more than 1700 depressed patients have been treated with one or more nights of total sleep deprivation (TSD; Wu and Bunney 1990). Review studies (Gillin 1983; Wu and Bunney 1990; Kuhs and Tölle 1991) agree that about 50–60% of the patients who underwent this treatment felt appreciably better on the day following TSD. They usually relapsed after subsequent sleep. Considerable within-subject variability in the response to TSD has also been noted (Fähndrich 1988): patients who do not respond to TSD initially may do so later, and those who do respond initially may not do so later. Thus, the potential *susceptibility* to TSD as a temporary antidepressant seems to be widespread among depressed patients. This susceptibility is not restricted to classical 'endogenous' depressions: beneficial

effects have also been reported in 'neurotic' depressions, although these are generally less marked and frequent (Gillin 1983; Fähndrich 1988; Wu and Bunney 1990; Kuhs and Tölle 1991), in schizophrenic patients with a post-psychotic depression (Fähndrich 1988), in women with premenstrual depression (Parry and Wehr 1987), in depressive pseudodementia (Letemendia *et al.* 1986; Buysse *et al.* 1988; Southmayd 1989), and in depressed patients with Parkinson's disease, whose motor symptoms were reported to improve also (Bertolucci *et al.* 1987). Patients with panic disorder (Roy-Byrne *et al.* 1986) and patients with obsessive-compulsive disorder (Joffe and Swinson 1988) have not been found to benefit from TSD. In schizophrenia TSD appears to improve 'negative symptoms' and to provoke 'positive symptoms' (Wehr 1990). A clear beneficial effect of TSD thus seems to be typical for the depressed state.

As yet, no satisfactory explanation of this effect has been found (van den Hoofdakker and Beersma 1988; Kuhs and Tölle 1991). Most explanations are sought in biorhythmic

Correspondence: W. van den Burg, Department of Neuropsychology, CMC I-3, AZG, Oostersingel 59, 9713 EZ Groningen, The Netherlands. Fax: +31/50 696737.

desynchronizations and disturbances which are supposed to be basic to the depressive symptomatology and which would be temporarily adjusted by sleep deprivation (Pflug and Tölle 1976; Wehr and Wirz-Justice 1981; Fährdrich 1988), and/or in depressogenic abnormalities related to the sleep process *per se* (Borbély and Wirz-Justice 1982; Beersma *et al.* 1985; Wu and Bunney 1990). Another approach, possibly compatible with other theories (van den Hoofdakker and Beersma 1988; van den Hoofdakker *et al.* 1990), has been based on the concept of behavioural and experiential activation or arousal. According to the classical view, a continuum of arousal, ranging from deep sleep or coma on one extreme to panic-stricken terror or great excitement on the other, is a basic dimension determining acting and feeling (Duffy 1962). In line with a theory of Zung *et al.* (1964; Zung 1969), and with theories of the general influence of TSD on normal subjects which were current at the time, van den Burg and van den Hoofdakker (1975) surmised that depressed patients are in an unremitting state of 'inner tension', i.e. over-arousal, and that TSD brings this back to more adequate levels. The results of several studies are in agreement with an over-arousal hypothesis (Gillin 1983; Bouhuys *et al.* 1989). In contrast, Post *et al.* (1976) and Gerner *et al.* (1979) consider the possibility that severely depressed patients are typically *hypoaroused*, and that they are temporarily activated and mobilized by the stress that TSD entails. Post *et al.* (1976) note that a variety of situations involving stress (including electroconvulsive shock therapy, physical illness and sudden environmental crises) have been related to improvement in depression. The purpose of the present study was to further explore the possibilities of an arousal explanation of the antidepressant effects of TSD. We will draw heavily upon psychological theories and findings relating to normal subjects.

The two arousal explanations differ on two important points. The first is whether TSD serves as an activator or as a de-activator, and the second is whether the depressed mental state is essentially one of hyper- or hypoarousal—or at least whether the hyper- or hypoarousal *side* of depression is affected by TSD. In terms of the typical depressive symptoms and complaints, both aspects are present at the same time: on the one hand there is continuous 'inner tension', related to feelings of guilt, worthlessness, anxiety, helplessness, inadequacy, resentment and the like, and on the other there is psychomotor retardation and lack of 'drive', mirrored in complaints such as listlessness, anhedonia, impotence and tiredness. In mild, non-clinical depression, tension and lack of energy tend likewise to coexist (Thayer 1989). This coexistence, however, suggests that a unidimensional concept of arousal is inadequate, or at least insufficient, in relation to depression. In recent years, in particular, it has been emphasized in various areas of research that 'arousal' may be defined and operationalized in several different, often poorly matching, ways and that it is certainly not unidimensional (e.g. Hockey and Hamilton 1983; Levenson

1983; Neiss 1988; Thayer 1989). Sleep deprivation studies have also shown the complexity of 'arousal' (Broadbent 1971; Kahneman 1973; Eysenck 1982; Sanders 1983). While arousal theorists generally agree that TSD is initially and primarily de-arousing, with the potential consequence of some detrimental effects on behaviour, it is also acknowledged that sleep-deprived subjects may sometimes show signs of high, instead of low arousal when they have to perform a demanding task or meet a stressful situation (Kahneman 1973; Eysenck 1982). On the basis of such findings, it is thus conceivable not only that the antidepressant effects of TSD are achieved by its common, de-arousing influence, with possible tension reduction as the first and foremost result, but also that the effects have primarily to be sought in an activating process, triggered by the efforts of the depressed patient to fight fatigue and 'sinking away'.

To elucidate these issues, the present study was directed at documenting the relationship between the antidepressant response to TSD and changes in arousal, as indicated by patients using the Activation Deactivation Adjective Check List (AD ACL) developed by Thayer (1967). The merits of assessing states of internal arousal by means of self-report data, relative to those of other measurements, have been discussed by Thayer (1970), Mackay (1980) and, in particular, in Thayer's recent book (1989). Factor-analytic studies of the AD ACL in normal subjects likewise did not evidence a single, unitary arousal continuum but, instead, consistently revealed four factors (Thayer 1986). In many studies, however, these factors could be reduced to two bipolar dimensions, 'tension-arousal' and 'energy-arousal', which appear to be correlated in a complex way (see Discussion). In some applications of the AD ACL the four factors have been used, in other the two dimensions.

The first question addressed in the present, longitudinal study was: can changes in the AD ACL self-ratings of depressed patients who respond to TSD (and relapse after subsequent sleep) be adequately summarized by means of the four factors and two arousal dimensions found in Thayer's studies? To answer this question, a recently developed method of component analysis was used to determine whether the structure of change was the same for *each individual* patient who responded to TSD. On the basis of the results, the second question was: to what extent and in what way is the pattern of response and relapse related to changes in self-rated arousal? The findings are considered in relation to the two basic issues underlying the different arousal explanations discussed above. A new interpretation of what happens when a depressed patient responds to TSD is offered. The present investigation continues a line of research on the possible role of dimensions of arousal in the mood response to TSD (Bouhuys *et al.* 1989, 1990a, b; van den Hoofdakker *et al.* 1989). Changes in self-rated arousal were studied by van den Hoofdakker *et al.* (1989) and Bouhuys *et al.* (1990a). In these studies, however, TSD was applied once, while the two-dimensional structure of the

AD ACL revealed in Thayer's research was presupposed. Responders to TSD appeared to experience both a reduction in 'tension arousal' and an increase in 'energy arousal'. In the present investigation TSD was applied four times.

METHODS

Patients and procedure

Consecutively admitted patients were considered for participation if their self-ratings on the Beck Depression Inventory (Beck *et al.* 1961) exceeded 16 on the Monday morning of the first week in which TSD might be applied; this was regarded as indicative of a moderate to severe depression. Such patients were interviewed in order to make a DSM III diagnosis and to rate depression severity by the Hamilton Rating Scale for Depression (first 17 items only; Hamilton 1967, 1986). If a serious depression dominated the clinical picture, the patients were asked to participate. Written consent was obtained. The study involved 23 subjects; particulars are given below.

For two consecutive weeks, TSD was applied during the nights of Tuesday to Wednesday and of Thursday to Friday. The study was conducted within the framework of a separate investigation in which, using a randomized cross-over design, the patients stayed up in the dimly lit living room of the ward during one week, and in a separate room where they were exposed to bright light during another week. Overall, the antidepressant effects of TSD did not differ greatly in the two conditions (van den Burg *et al.* 1990). Naps were prohibited during the TSD nights and on subsequent days. From Tuesday to Saturday, daily at 09.00 hours, 17.00 hours and 22.00 hours, and during the TSD nights at 01.00 hours and 05.00 hours, the patients rated themselves using von Zerssen's 'Adjective Mood Scale' (form AMS'; von Zerssen 1976, 1986) and Thayer's AD ACL.

The von Zerssen scale is a standard scale for self-rated depression with scores ranging from 0 (not depressed) to 56. It is particularly suited for frequent use at short intervals. The Dutch translation has been shown to be psychometrically reliable (Elsenga 1988). The AD ACL consists of 20 activation-descriptive adjectives, each of which is rated on a four-point scale according to how well the adjective describes one's momentary feelings. In its Dutch version the four points have the meaning: 'yes, definitely', 'yes, a bit', 'no, not really', and 'no, definitely not'. The items are rendered in Fig. 1, grouped according to the four factors and the two arousal dimensions that they were found to represent in Thayer's studies. The factors/scales have been labelled as in Thayer (1986), but two prefixes '(non-)' have been added to clearly indicate that a high score always means a high level of arousal on the factor concerned. Some patients indicated difficulties in interpreting the bracketed adjectives as feelings, and the scores on these items often appeared to correlate poorly with those on others. In the analyses to be presented, only the 16 'unproblematic' items have been used. Whenever we refer below to Thayer's factors or to the scale scores (maximum 16, minimum 4), the label will be capitalized (e.g. Tension) or abbreviated as in Fig. 1 (e.g. Te).

As in van den Burg *et al.* (1990), we defined 'responders' as patients who responded to at least two of the four TSDs, and a 'response' as a mean von Zerssen score on the day after TSD of 6 or more points less than the mean score on the day before. Using these definitions, there were eight responders, five men and three women, with a mean Hamilton score of 22.4 (s.d. = 4.0, range 18–28, one score missing) and a mean age of 52.1 years (s.d. = 11.5; range 37–68 years). By requiring a 'response' to occur at least twice we intended to ensure that: (a) the improvements after TSD were indeed caused by TSD, and were not unrelated fluctuations in the state of the patients, and that (b) sufficient substantial changes in the AD ACL scores

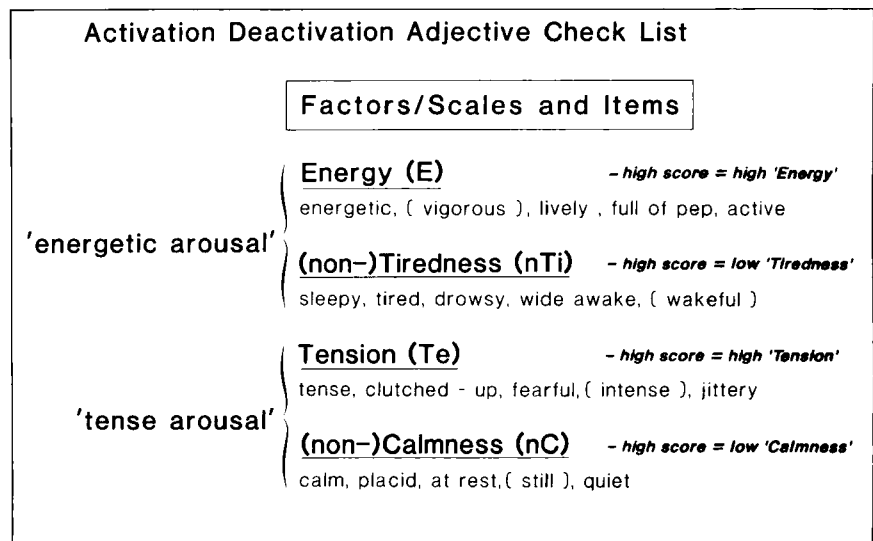


Figure 1. The structure of the Activation Deactivation Adjective Check List (AD ACL), as this appeared from Thayer's studies. Subsuming two arousal dimensions, four factors/scales are discerned, each consisting of five items. The parenthesized items have not been used in the present study.

were present to reliably assess the structure of these changes in relation to the antidepressive effect of TSD (see below). Three responders responded all four times, two responded three times, and three responded twice. Three were medication-free and five were receiving tricyclic antidepressants in an unvarying dosage. A 'response' occurred once in four of the 15 non-responders: seven men and eight women, with a mean Hamilton score of 24.6 (s.d. = 7.3, range 15–38) and a mean age of 44.9 (s.d. = 14.8, range 24–68 years). Two were medication-free; two were receiving lithium and 11 were receiving tricyclic antidepressants and/or neuroleptics in an unvarying dosage. More details on the medication are given in van den Burg *et al.* (1990). Seven responders and 14 non-responders met the DSM-III criteria for major depression (296.2 or 296.3); one responder was classified as an atypical depression (296.8); and one non-responder as an atypical bipolar disorder, depressive phase (296.7).

Component analyses

Each subject had completed the 16 items of the AD ACL 38 times in total. Focusing on the group of eight responders, the analysis for assessing the adequacy of Thayer's factors and dimensions for representing the course of these scores proceeded in two steps. In step 1 it was examined whether the factor structure of the changes was the same for each individual responder, and in step 2 whether the factors revealed were in essence equal to (combinations of) Thayer's factors. A few analyses were likewise performed on the data of the non-responders, but these did not change much over time and thus were not well suited for determining a structure (see Results section).

In step 1 the results of principal component analyses (PCA), performed separately on each data set of a responder, were compared with the results from a simultaneous component analysis, or SCA (Millsap and Meredith 1988; Kiers and ten Berge 1989). SCA is a recent extension of PCA. As with PCA, a few components are computed as weighted sums of the variables measured, such that these components explain as much of the total variance in the scores as possible. The extension is that two or more data sets, instead of just one, are considered simultaneously while the analysis is performed under the constraint that the weights for computing the components be the same for all data sets. If for each responder the amount of variance explained by performing a separate PCA on his/her data set hardly differs from the amount of variance explained when applying SCA, the components in the eight data sets can be considered as the same (a formal statistical test does not exist). Whereas the PCAs were based on 38 completions of the AD ACL, an SCA was based on 304 completions.

For step 2 the components resulting from SCA were first subjected to a varimax rotation and then to an oblique rotation. Subsequently, the item weights defining the rotated components were inspected for determining which

(combination of the) Thayer factors resembled these components most closely; for example, in a two-component analysis, nTi and $Te + nC - E$. The procedure for establishing the degree of similarity was to replace the item weights defining the components by item weights 1, 0 or -1 in conformity with the suggested (combinations of) Thayer factors, and to compare the amounts of variance explained by the SCA components with those obtained by the Thayerian composites. If these amounts agree closely for all responders, the same (combinations of) Thayer factors are apparently adequate for representing the course of self-related arousal of each of them. (Again, no formal statistical test is available.) The procedure is a version of the multiple group method of confirmatory factor analysis (Gorsuch 1988, pp. 80–93).

The analyses to be presented were based on AD ACL scores which were standardized within each set of data. This is the common procedure. We also employed some other types of scores, such as unstandardized deviation scores from the means, but all analyses revealed the same basic structure of the components. The analyses were carried out by means of an interactive computer program which is commercially available in a now extended form (Kiers 1990). The computational method has been described by Kiers and ten Berge (1989).

RESULTS

Responders

Table 1 shows the PCA and SCA results for the eight responders, using 1, 2, 3 and 4 components for 'summarizing' the self-ratings on the AD ACL. In all four analyses the percentages of variance explained by PCA, by SCA and by Thayerian composites agree well, indicating that the same components render the course of the scores for all responders adequately, and that these components were well translatable as composites of Thayer's four factors. In the one-component analysis, this component appeared to be basically identical to the composite $Te + nC - E$, a continuum with, at one end, high scores on Tension and non-Calmness and low scores on Energy, and at the other, low scores on Tension and non-Calmness and high scores on Energy. The SCA weights for the Tiredness-items were close to zero in this analysis. Tiredness, however, emerged as the second dimension in the two-component analysis, next to the ' $Te + nC - E$ ' dimension. The two-component analysis in particular yielded percentages of explained variance which agreed extremely well. They were also substantially higher than those of the one-component analysis. Thus, at least these two components appear to be necessary to adequately represent the course of the self-ratings. In the three-component analysis the ' $Te + nC - E$ ' continuum broke up in the Energy factor and in the 'tension arousal' dimension ($Te + nC$). In the four-component analysis, all four Thayer

Table 1 The structure of changes in the AD ACL scores of responders to TSD: percentages of variance explained by principal components, simultaneous components, and composites of Thayer's factors

	Using 1 component			Using 2 components			Using 3 components			Using 4 components		
	PCA	SCA	Te + nC - E	PCA	SCA	Te + nC - E, nTi	PCA	SCA	Te + nC, E, nTi	PCA	SCA	E, nC, Te, nTi
pat. 1	31.1	30.8	30.8	49.9	49.3	49.1	59.8	57.8	56.9	67.9	66.3	65.5
pat. 2	38.0	37.2	35.9	55.7	55.4	54.8	70.9	70.2	69.6	77.6	75.9	74.2
pat. 3	59.7	58.8	57.3	72.7	71.5	70.5	77.9	76.7	76.6	82.5	80.0	79.2
pat. 4	46.0	45.8	45.8	60.8	60.4	60.3	68.4	66.7	66.1	75.3	74.1	72.5
pat. 5	72.8	72.8	72.6	90.0	89.9	90.0	93.2	92.0	91.4	95.7	93.3	91.9
pat. 6	37.4	35.8	36.1	49.3	48.3	47.3	58.2	56.3	54.0	64.8	61.1	58.8
pat. 7	44.3	44.0	43.2	59.4	59.1	59.1	67.6	66.8	66.8	73.0	71.7	71.7
pat. 8	60.5	60.2	60.4	84.1	84.0	84.0	88.3	87.4	87.6	91.0	89.7	89.5
Average	48.7	48.2	46.3	65.2	64.8	64.4	73.0	71.7	71.1	78.5	76.5	75.4

factors emerged as separate components. The latter two analyses both yielded additional amounts of explained variance which were not inconsiderable but also were not very marked. Five- and six-component analyses each explained only an additional 4% of variance, while the weights were not well interpretable. In summary, both 2, 3 and 4 (Thayerian) components were acceptable for summarizing the course of the AD ACL scores.

For each responder, Thayer's scale scores and their composites revealed by the component analyses were correlated with each other and with self-rated depression (von Zerssen scale scores). The general pattern in the individual correlation matrices was the same. Table 2 gives the mean values. As appears from this table: (a) non-Calmness, Tension, lack of Energy and self-rated depression are closely related; (b) Tiredness is hardly related to any of the other variables; (c) self-rated depression correlates most strongly with the composite score $Te + nC - E$.

Figure 2 shows the course of the scores on the four Thayer scales. As in the other Figures to be shown, the scores of the first week have been averaged with those of the second week. The Figure indicates that after TSD the responders felt on average both calmer and less tense and, seemingly to a similar degree, more energetic. There is no suggestion whatsoever from this graph, nor from inspection of the individual data, that any one of these changes for the better preceded any other. In Fig. 3 the Tiredness scores, the $Te + nC - E$ scores and the von Zerssen scores are rescaled to a common scale of 'well-being', ranging from 0 (depressed, tired) to 100. It shows that the course of

$Te + nC - E$ is virtually a copy of the course of self-rated depression. It shows also, as does Fig. 2, that the course of the Tiredness scores was different, the subjects feeling on average more tired and sleepy after TSD, but not in parallel to the other changes. This point will be further considered in the Discussion.

Non-responders

Some analyses carried out on subsets of the 15 data sets of the non-responders (the program could not handle all data sets simultaneously) did not suggest that the components were different from those for the responders. As might be expected, however, the results were more 'messy'. Since the self-ratings of the non-responders on most of the items did not change a great deal, and thus contained relatively much 'random' fluctuation, smaller percentages of variances were explained by PCA, and these were less well approximated by SCA and by the composites of Thayer's factors.

Figure 4 gives the analogue of Fig. 2 for the non-responders. Tiredness seems globally to follow a similar course as in the group of responders. The graph of the course of self-rated depression (not shown) is as flat as the graphs for Calmness, Tension and Energy, and thus also as that for the $Te + nC - E$ scores. The analogue of Fig. 3, giving no additional information, has been omitted.

For a statistical comparison of the self-ratings of the responders and non-responders on the four Thayer scales, the mean changes on the days after TSD relative to the mean scores on the three other, 'non-TSD', days were considered, as were the mean scores on the non-TSD days

Table 2 (Composites of) Thayer's factors and self-rated depression: mean correlations in responders to TSD

	E	nTi	Te	nC	(1)	(2)	D
Energy (E)	1.00						
(non-)Tiredness (nTi)	0.17	1.00					
Tension (Te)	-0.63	-0.14	1.00				
(non-)Calmness (nC)	-0.70	-0.11	0.69	1.00			
Te + nC (1)	-0.74	-0.12	0.89	0.93	1.00		
Te + nC - E (2)	-0.89	-0.15	0.84	0.90	0.96	1.00	
Depression (D)	-0.81	-0.23	0.78	0.76	0.84	0.89	1.00

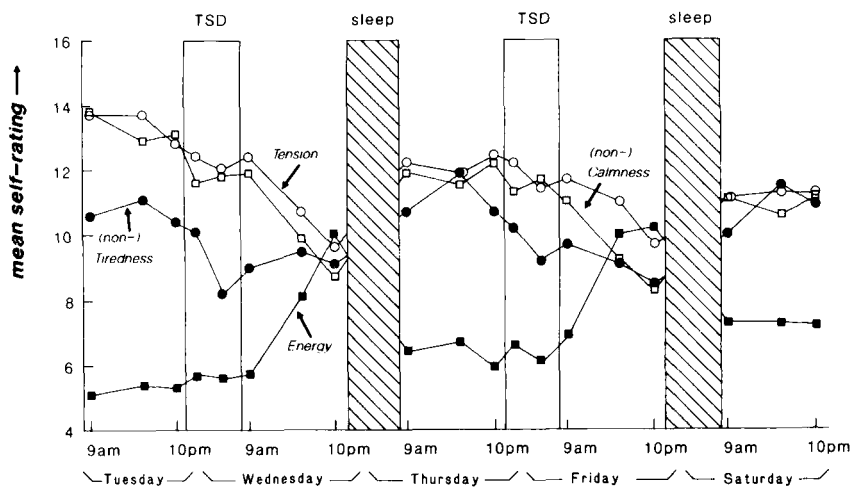


Figure 2. Responders to TSD ($n = 8$). Mean course of self-rated arousal on the four Thayer scales (see Fig. 1). Averages of week 1 and week 2.

per se. Two-sided tests were applied. While the responders improved significantly more than the non-responders on the days after TSD with respect to Calmness, Tension, Energy and the $Te + nC - E$ scores ($P < 0.001$, Mann-Whitney tests), there was no significant difference regarding the changes in Tiredness; both groups felt, apparently to a similar degree, more tired and sleepy on the days after TSD ($P < 0.01$, Wilcoxon's signed ranks test; pooled data). The standard deviation of the changes in Tiredness was higher in the group of responders than in the group of non-responders (2.3 vs 1.2; $P < 0.05$, F -test). On the non-TSD days, there were no significant differences between responders and non-responders in terms of Calmness, Tension, Energy and the $Te + nC - E$ scores. There was, however, a tendency for the responders to indicate less Tiredness than the non-responders on the non-TSD days ($P < 0.07$, Mann-Whitney test; $P < 0.04$, t -test).

Responses vs non-responses

Corresponding to the component analyses, Figs 2 and 3 were based on all data of the responders, including the 8

times (out of 32 TSDs) that no response occurred according to our definition. Likewise, Fig. 4 was based on all data of the non-responders, including the 4 times (out of 60 TSDs) that a 'response' occurred. Considering each TSD as an independent trial, comparisons of 'responses' to 'non-responses' showed, with the exception of one anomaly, the same differences and similarities in the course of Thayer's factors and of the $Te + nC - E$ dimension as the comparisons of responders to non-responders (Mann-Whitney and Wilcoxon tests for the average pre-TSD/post-TSD differences and for the average pre-TSD scores; F -test for standard deviations). Table 3 shows the course of the scores on the $Te + nC - E$ dimension and on the Tiredness factor, rescaled as in Fig. 3. The anomaly was that the mean pre-TSD $Te + nC - E$ scores (rescaled) appeared to be higher for the non-responses than for the responses, indicating less depression ($P < 0.05$).

Unless indicated otherwise, we will not distinguish between (non-)responders and (non-)responses in the Discussion below, but for the sake of brevity only refer to responders and non-responders.

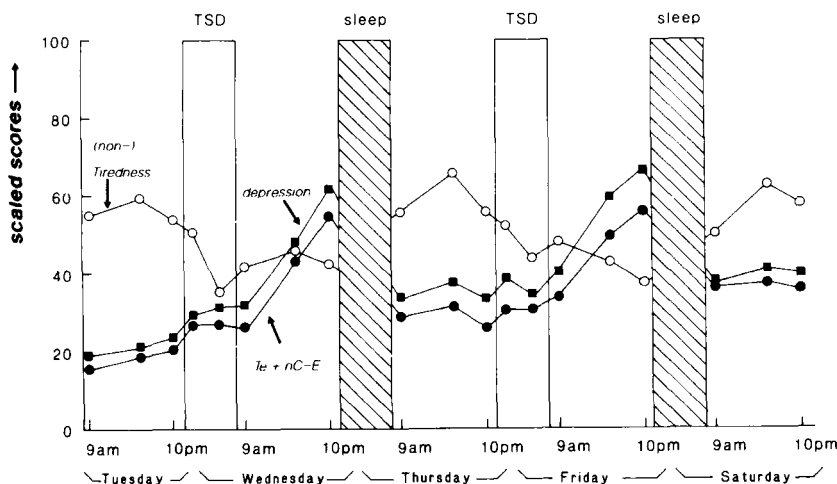


Figure 3. Responders to TSD ($n = 8$). Three kinds of self-rating data, rescaled to a common scale of 'well-being' ranging from 0 to 100. Averages of week 1 and week 2. Note that using this scale, high scores derived from the depression self-ratings (von Zerssen scale) and from the $Te + nC - E$ scores (see text) correspond to little depression.

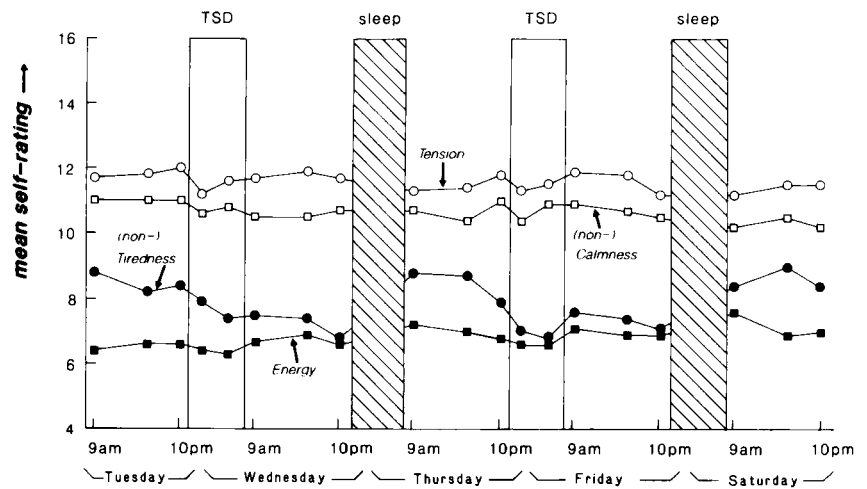


Figure 4. Non-responders to TSD ($n = 15$). Mean course of self-rated arousal on the four Thayer scales (see Fig. 1). Averages of week 1 and week 2.

DISCUSSION

The four-component analyses of the AD ACL scores indicated that Thayer's four factors were adequate for summarizing the changes in self-rated arousal of the responders to TSD. However, a simpler structure could also satisfactorily account for these changes. The simplest was a two-dimensional structure, one dimension representing feelings of Tiredness, and the second dimension a continuum with, simultaneously, feelings of Tension, non-Calmness and lack of Energy at one end, and feelings of Energy, Calmness and non-Tension at the other (the $Te + nC - E$ dimension). For the interpretation of the results, however, it does not matter much whether one would prefer in the first instance a four-, three-, or two-dimensional structure. If, for example, one were to consider a four-component solution best, it would have to be added that Tension, Calmness and Energy were closely related (Table 2), which would then lead to a similar

conceptual structure of the changes to that if a two-dimensional structure had been assumed. Thus, for the present discussion a two-dimensional view is the most direct. Since the components could be considered to be the same for each individual responder, it is apparent that medication, type of patient, or number of 'responses' did not affect the composition of the components. There was also no reason to suspect that these were different in the group of non-responders.

The two dimensions revealed were different from the 'energy arousal' and 'tension arousal' dimensions to which Thayer's four factors usually appeared to reduce (Fig. 1). Thus, these dimensions do not appear to be well suited for representing the course of self-rated arousal of depressed patients during and after TSD, contrary to what we assumed in previous research (Bouhuys *et al.* 1990; van den Hoofdakker *et al.* 1989). It is worth noting that the AD ACL data do not suggest that the patients rated their condition according to one global, aspecific continuum of

Table 3 Responses vs non-responses: mean self-ratings (s.d.) on the $Te + nC - E$ dimension and the (non-)Tiredness factor

		Responses ($n = 28$)		Non-responses ($n = 64$)	
		$Te + nC - E$	(non-)Tiredness	$Te + nC - E$	(non-)Tiredness
Pre - TSD	09.00 hours	22.1 (18.4)	56.6 (33.6)	33.9 (20.3)	40.1 (24.1)
	17.00 hours	23.0 (21.0)	58.9 (33.3)	35.1 (21.4)	40.4 (24.6)
	22.00 hours	20.0 (17.9)	52.7 (31.0)	33.5 (23.0)	36.7 (22.6)
	Average	21.7 (17.6)	56.0 (29.7)	34.2 (20.8)	39.1 (19.6)
	01.00 hours	26.1 (21.1)	50.9 (29.4)	36.1 (22.9)	30.5 (20.7)
Post - TSD	05.00 hours	28.6 (24.7)	42.0 (31.8)	33.4 (20.4)	25.7 (20.4)
	09.00 hours	31.2 (22.7)	50.3 (31.1)	33.6 (20.7)	27.9 (21.2)
	17.00 hours	48.0 (16.9)	47.0 (32.3)	35.6 (21.2)	28.0 (19.8)
	22.00 hours	56.2 (17.3)	45.2 (31.8)	36.1 (20.7)	23.2 (19.2)
	Average	45.1 (12.1)	47.5 (27.3)	35.1 (19.6)	26.4 (17.6)
Post - Pre		23.4 (17.1)	-8.5 (24.3)	0.9 (7.9)	-12.7 (14.3)

Note: As in Fig. 3, scores are rescaled to a common scale of 'well-being' ranging from 0 (depressed, tired) to 100; Average = average of 09.00 hours, 17.00 hours and 22.00 hours scores; Post - Pre = difference between pre - TSD and post - TSD averages.

subjective discomfort; the possibility of such an interpretation might hamper any other interpretation (Tellegen 1985; van den Hoofdakker *et al.* 1989). The fact that the responders reported to sense after TSD increased Energy against a background of increased Tiredness (Fig. 2) indicates this most clearly. The (non-significant) suggestion of a smaller increase in Tiredness when responding to TSD than when not responding, together with a greater standard deviation of the differences scores (Table 3), may reflect, however, that the simultaneity of these feeling-states was sometimes confusing to the patient.

The nature of the antidepressant response to TSD

The course of improvement and relapse of the responders to TSD (von Zerssen scale scores) was nearly completely translatable in terms of changes on the $Te + nC - E$ continuum (Table 2, Fig. 3). The nature of this continuum reaffirms that depression, in arousal terms, is multidimensional, having both a tension and non-energy aspect. (This multidimensionality may be an important reason why psychophysiological research regarding depression often yields results which are difficult to interpret; Lader 1983). The nature of the $Te + nC - E$ continuum indicates further that unidimensional arousal explanations for the antidepressant effects of TSD are insufficient (see, however, below). An explanation in terms of 'under-arousal'—i.e. depressed patients are chronically under-aroused and the stress of TSD forces them to function at higher, more adequate levels—is insufficient because it does not, *per se*, explain the reduction in felt tension and the increase in calmness. An explanation in terms of 'over-arousal'—i.e. depressed patients are chronically over-aroused and TSD lowers arousal to more adequate levels—is insufficient because it does not, *per se*, explain the increase in felt energy. Furthermore, the decrease in Tension and non-Calmness seemed about as great as the increase in Energy, while no trace of an order in the occurrence of these changes could be detected (Fig. 2). Although an order cannot be excluded—the changes may follow each other in a very short interval—the close coupling suggests one underlying process.

How, then, to conceptualize this process? As appears from Thayer's studies involving normal subjects, 'energy arousal' and 'tension arousal' are positively correlated at low to moderate levels; at low levels, an extra bit of tension or anxiety appears to be energizing (Thayer 1989). At high levels on either of these dimensions, however, 'energy arousal' and 'tension arousal' are negatively correlated. Leaving aside the course of Tiredness (see below), this was the pattern in the self-ratings of the responders. The most natural explanation for this inverse relationship is that strong feelings of tension may inhibit feelings of energy, while low levels of energy may easily lead to tension because one more quickly feels not strong enough to cope (Thayer 1989). However, these two effects may apparently reinforce each other and, without intervention, lead eventually to a

continuing and distressing state of deadlock. From this perspective, our data suggest that what happens when a depressed patient responds to TSD, may well be understood as a process of 'deblocking' or *disinhibition*.

The underlying idea that an essential characteristic of the depressed state is some sort of block in feeling and thinking, involving two or more motivational processes, is an old one (Lewis 1934). A view recently advanced by Fowles (1988) is closely related to ours. On the basis of Gray's motivational theory (e.g. 1987), he supposes that the distinguishing feature in depression is a reciprocal antagonism between an appetitive motivational system (related to feelings of energy) and an aversive motivational system (related to tension and anxiety). See Fowles (1988) and Gilbert (1984; see also below) for (more or less) similar theories. In terms of the typical symptoms and preoccupations of depressed patients, this view suggests that TSD may 'loosen' the block where, in a continuing circle, strong feelings of guilt, inadequacy, anxiety and sometimes resentment (the 'over-aroused', tension side of their mental state), lead to feelings of impotence, anhedonia and psychomotor retardation (the 'under-aroused', non-energy side of their mental state), and vice versa. It does not happen often, but Wu and Bunney (1990) refer to ten reports in which mania or hypomania have been described as a result of TSD. Such an event may readily be interpreted as an 'overshoot' of a disinhibition process. It seems to occur hardly more often in bipolar than in non-bipolar patients (Wu and Bunney 1990). Wehr *et al.* (1987) found evidence that an extended period of sleep reduction is a final common pathway in the genesis of mania. With reference to the evidence that TSD in schizophrenia tends to improve 'negative' symptoms and to provoke 'positive' symptoms, Wehr (1990) remarks (p. 66): "it might be more accurate to describe the effects of sleep deprivation more generally as improving inhibited states and provoking excited states". Our view, independently arrived at from a different angle, closely fits in with this reading.

An explanation

One conclusion from our data might be that tiredness and sleepiness have nothing to do with the antidepressant effect of TSD. Both responders and non-responders indicated, seemingly to a similar degree, more Tiredness after TSD, while the course of Tiredness was hardly correlated with any change in self-rated depression. However, we feel that it is more likely that the increase in tiredness and sleepiness is very important. This is always the most conspicuous effect of sleep loss and points, in some way, to a certain fatigue of the brain. "With the exception of the brain, [...] sleep deprivation is surprisingly uneventful for the rest of the body" (Horne 1988, p. 97; see further below). Given that TSD induces cerebral fatigue in depressives, as it does in normal subjects, we deem it plausible and parsimonious to suppose that this fatigue plays a key role, not in a one-to-one causal relation with the antidepressive effect, but

as a *matrix* on which the antidepressive effect *may* develop. This view allows for the intra-individual variability of the response, and is consistent with Figs 2–4 and Table 3 which clearly indicate that the patients tended to sense an increase in Tiredness before any marked antidepressive effect. The latter point is in agreement with previous observations (Pflug 1976; Rudolf and Tölle 1978).

It should be noted that we assume that the course of Tiredness at least *partly* reflects some fatigue of the brain. Subjective fatigue depends on many factors. For one thing, tension and tiredness often go together (Thayer 1989), and fatigue is a common complaint of depressed patients. The Tiredness self-ratings on the non-TSD days indicated that this applied to our patients also, to some extent. The responders indicated less Tiredness than the non-responders on these days, but any interpretation of this, possibly accidental, finding must await further corroboration. (The same applies to the ‘anomalous finding’ of lower pre-TSD $Te + nC - E$ scores, indicating more depression, when responding than when not responding; Table 3.) A second complexity is that subjective fatigue during and after TSD of normal subjects shows, apart from a monotonic increasing trend, a pronounced 24-h oscillation, with a peak in the small hours and a lowest point in the late afternoon/early evening (Åkerstedt 1979). A similar, though not as marked circadian rhythm can be perceived in our Tiredness data. There are arguments to suppose, however, that the circadian component is not much related to cerebral fatigue (Horne 1988). Assuming that only the monotonic component is relevant, a clear link can be noted between increased Tiredness, increased fatigue of the brain, and the accumulation of Borbély’s factor S (Borbély 1982; Daan *et al.* 1984). It may also be noted that the role we assign to the increase in tiredness/sleepiness can be considered as a modified ‘arousal–reduction’ hypothesis, if the concept of arousal is given a much more restricted meaning than in the traditional sense.

For a psychological explanation as to why and how cerebral fatigue may lead to disinhibitory, antidepressive effects, the way sleep loss ordinarily affects mental and behavioural functioning must be considered. With respect to task performance, Johnson (1983, p. 122) characterized the most vulnerable tasks as follows: “In summary, the long, work-paced, complex tasks with high attention and vigilance requirements and which do not provide information to the subject on how well he is performing can be expected to show higher sensitivity to total sleep loss”. Meddis (1982) stresses the decrease in interest and motivation to initiate and sustain any activity asked for. Wilkinson (1965, p. 423) noted that, where formal tests may not show much of an effect of TSD, a certain disorganization of behaviour is often observable during the periods when *no* such tests are being taken. According to Naitoh, who studied the contingent negative variation after TSD, the sleep-deprived brain “lives from moment to moment, without pre-planned preparation” (cited in Horne 1988, p. 75). All these effects

have in common reduced active self-regulation of one’s mental and behavioural processes, either because of disinclination (the motivational aspect), or inability, or both. We consider it plausible that this general effect in depressed patients forms the basis for a decrease in their inhibitory preoccupations, an increase in unconcern, and thereby a ‘de-blocking’ of their feeling-state. The same general impact of TSD may lie at the root of its effects in schizophrenia (see before).

It is difficult to assess from the literature to what extent comparable disinhibitory effects may occur in normal subjects. Any such effects are difficult to measure precisely, and easily hidden by prominent sleepiness (Gillberg and Åkerstedt 1981). Furthermore, mood changes in the sphere of ‘euphoric disinhibition’ cannot be expected to occur frequently within the rather unnatural confines of the usual, strictly controlled sleep deprivation experiment that requires the sleepy subjects to occupy themselves with all kinds of activities they are not disposed to (Meddis 1982). Irritability is “a classic symptom” of such subjects (Murray 1965, p. 218). Nevertheless, Murray (1965, p. 215) cites a few studies in which phenomena such as “euphoria” and “prolonged uproarious laughter” were occasionally observed. Meddis (1982), who at one time regularly deprived himself of sleep, clearly experienced effects in this direction, noting, for instance, aside from irritability, “moments of uninhibited levity in public” (p. 244). We ourselves are also well acquainted with the irritability and levity sleep loss may induce. According to our introspections, both these phenomena clearly bear the mark of a disinclination or disability to self-control. In our view, the anxiety and depression which are sometimes also observed in normal, sleep-deprived subjects (Murray 1965, Ch. 7) can best be understood as being related to the feedback-awareness of not being able to control one’s behaviour adequately. The sense of losing control may also well explain the worsening after TSD of a number of patients with panic disorder (Roy-Byrne *et al.* 1986); four of the 12 patients studied by Roy-Byrne *et al.* had a spontaneous panic attack on the day following TSD.

A clarification as to why the effects of only one night of sleep loss may be so marked in depressed patients, while these are generally not very striking in normal subjects, may be found in the instability of the depressed ‘brain state’. This may be inferred from the large intra-subject variability in the mood of many depressed patients (Lader *et al.* 1987), the mere existence of diurnal variations, the instability of these diurnal variations (Tölle and Goetze 1987; Gordijn *et al.* 1990), and anecdotal reports of how depressed subjects may experience a sudden worsening or lifting of their depression. Gilbert (1984, p. 199 ff.), who discusses some of these aspects, presented an interesting conceptual model of this instability. Resembling Fowles’ (1988) and our views discussed above, he supposes that two opposing motivations, having the character of approach and avoidance, are ‘at work’ in the response system of the depressed patient.

Using catastrophe theory, he demonstrates how major changes in the state of the patients may result from minor changes in the relative 'strength' of these motivations. It is interesting to note in this connection that there is evidence that patients who usually feel better in the evening in particular tend to respond to TSD (Roy-Byrne *et al.* 1984; Elsenga and van den Hoofdakker 1987; Reinink *et al.* 1990a,b). Thus, if the balance between the two opposing motivations already tends to change for the better during the day, there is a greater probability of further improvement by means of TSD.

The cerebral basis

In some recent, as yet unpublished and, as the authors stress, preliminary investigations, Wu and his colleagues studied localized cerebral glucose metabolism before and after TSD in normal and depressed patients (Gillin *et al.* 1990). The four depressed patients who responded to TSD were characterized by high pre-TSD activity in the cingulate which was significantly reduced after TSD. The investigators interpret their findings as meaning that TSD probably dampens subcortical arousal systems, and that cortical function is probably affected in some secondary way (Gillin, pers. comm.). From these and our data it might be conjectured that the increased Tiredness after TSD is associated with a dampening of subcortical arousal systems.

On the other hand, Horne (1978, 1988) has a strong case in claiming that sleep loss in humans has primarily a cortical impact (probably in contrast to the impact in rats; cf. Horne 1988 and Rechtschaffen 1990). After extensive reviews of the sleep deprivation literature, Horne (1988; p. 98) comes to the same general conclusion as Kleitman (1963, p. 229) on the basis of the early studies: "They suggest a fatigue of the higher levels of the cerebral cortex—the levels that are responsible for the critical analysis of incoming impulses and the elaboration of adequate responses in the light of one's previous experience". As Moruzzi (1966) pointed out, and Horne (1988, p. 143) stresses, the lower parts of the brain that regulate sleep and wakefulness do not seem to need sleep themselves. Kleitman's formulation concurs well with the psychological basis we proposed as underlying the antidepressant effect of TSD. This formulation and our analysis, however, further strongly suggest a particular involvement of the prefrontal cortex. In general terms, this is the part of the brain that organizes mental activities in relation to the planning and execution of behavioural programs (Luria 1973; Fuster 1989), while regulating 'drive' and motivation in the process (Stuss and Benson 1986). Its orbital regions appear to play a specific role in the inhibition of actions and drive (Stuss and Benson 1986, p. 243; Fuster 1989, p. 195). The beneficial effect of TSD in depression is perhaps specifically related to a reduction of over-inhibitory activity in these regions. A particular implication of the frontal areas in the effects of TSD was hinted at by Horne (1988, p. 55). A very recent review by him (Horne 1991,

appearing after completion of the earlier drafts of the present paper) has now brought together a wealth of neuropsychological evidence indicating that TSD indeed affects frontal lobe functioning especially.

Nevertheless, a significant role for the cingulate cortex in producing the antidepressant effects seems also to be compatible with our suppositions. It is the only cortical part of the classical 'emotional' circuit of Papez, and many studies have shown its implication (particularly of the anterior part) in anxiety-related inhibition of behaviour (Baleydier and Maguier 1980; Isaacson 1982). It is worth noting that both the anterior cingulate and the orbital prefrontal cortex are at present the main targets for psychosurgery in intractable depression (Valenstein 1980; Barlett *et al.* 1981; Donnelly 1985). There is also a notable link with Gray's theory that the descending pathway of the prefrontal cortex–cingulate cortex–septo-hippocampal system is an important route in bringing about behavioural inhibition (as he conceptualizes it) in anxiety disorders (Gray 1987, p. 338). Whatever the crucial route may be, however, it has to be noted that eventually the effects of TSD in depression are likely to produce quite complex changes in brain activity. The arousing (more Energy) and, conversely, the de-arousing (less Tension and more Calmness) effects of TSD, against a background of increased Tiredness, may involve the modulation of neural activity in widely distributed networks.

ACKNOWLEDGEMENTS

We are indebted to Mrs L. C. W. Dols and the nursing staff for their assistance in data collection, to Dr J. C. Gillin for his very helpful comments on an earlier draft of this paper, to Dr F. Heynick for checking the English, and to Dr H. A. L. Kiers for adapting his SCA program for use in the present study.

REFERENCES

- Åkerstedt, T. Altered sleep/wake patterns and circadian rhythms. *Acta Physiol. Scand.*, 1979, Suppl. 469: entire.
- Baleydier, C. and Maguier, F. The duality of the cingulate gyrus in the monkey: neuroanatomical study and functional hypothesis. *Brain*, 1980, 103: 525–554.
- Bartlett, J., Bridges, P. and Kelley, D. Contemporary indications for psychosurgery. *Br. J. Psychiatry*, 1981, 138: 507–511.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. E. and Erbaugh, J. K. An inventory for measuring depression. *Arch. Gen. Psychiatry*, 1961, 4: 561–571.
- Beersma, D. G. M., Daan, S. and van den Hoofdakker, R. H. The timing of sleep in depression: theoretical considerations. *Psychiatr. Res.*, 1985, 16: 253–262.
- Bertolucci, P. H., Andrade, L. A., Lima, J. G. and Carlini, E. A. Total sleep deprivation and Parkinson disease. *Arq. Neuropsiquiatr.*, 1987, 45: 224–230.
- Borbély, A. A. A two-process model of sleep regulation. *Hum. Neurobiol.*, 1982, 1: 195–204.
- Borbély, A. A. and Wirz-Justice, A. Sleep, sleep deprivation and depression. *Hum. Neurobiol.*, 1982, 1: 205–210.

- Bouhuys, A. L., Beersma, D. G. M. and van den Hoofdakker, R. H. Observed behavior as a predictor of the response to sleep deprivation in depressed patients. *Psychiatr. Res.*, 1989, 28: 47-61.
- Bouhuys, A. L., Flentge, F. and van den Hoofdakker, R. H. Effects of total sleep deprivation on urinary cortisol, self-rated arousal and mood in depressed patients. *Psychiatry Res.*, 1990a, 34: 149-162.
- Bouhuys, A. L., Schutte, H. K. and Beersma, D. G. M. Relations between depressed mood and vocal parameters before, during and after sleep deprivation: a circadian rhythm study. *J. Affect. Disord.*, 1990b, 19: 249-258.
- Broadbent, D. E. *Decision and Stress*. Academic Press, London, 1971.
- Buyse, D. J., Reynolds, C. F., Kupfer, D. J., Houck, P. R., Hoch, C. C., Stack, J. A. and Berman, S. R. Electroencephalographic sleep in depressive pseudodementia. *Arch. Gen. Psychiatr.*, 1988, 45: 568-575.
- Daan, S., Beersma, D. G. M. and Borbély, A. A. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.*, 1984, 246: R161-R178.
- Donnelly, J., Psychosurgery. In: H. J. Kaplan and B. J. Sadock (Eds) *Comprehensive Textbook of Psychiatry/IV, Vol. 2*. Williams and Wilkins, Baltimore, 1985: 1563-1569.
- Duffy, E. *Activation and Behavior*. Wiley, New York, 1962.
- Elsenga, S. Een zelfbeoordelingsschaal voor depressie. *Tijdschr. Psychiatr.*, 1988, 30: 114-124.
- Elsenga, S. and van den Hoofdakker, R. H. Response to total sleep deprivation and clomipramine in endogenous depression. *J. Psychiatr. Res.*, 1987, 21: 157-161.
- Eysenck, M. W. *Attention and Arousal: Cognition and Performance*. Springer-Verlag, Berlin, 1982.
- Fähndrich, E. Chronobiologie der Depression: therapeutische und theoretische Aspekte des Schlafentzuges. In: M. Wolfersdorf, W. Kopitke and G. Hole (Eds) *Klinische Diagnostik und Therapie der Depression*. Roderer Verlag, Regensburg, 1988: 126-141.
- Fowles, D. C. Psychophysiology and psychopathology: a motivational approach. *Psychophysiology*, 1988, 25: 373-391.
- Fuster, J. M. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. Raven Press, New York, 1989 (second edition).
- Gerner, R. H., Post, R. M., Gillin, J. C. and Bunney, W. E. Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J. Psychiatr. Res.*, 1979, 15: 21-40.
- Gilberg, M. and Åkerstedt, T. Sleep deprivation in normals—some psychological and biochemical data from three studies. In: W. P. Koella (Ed.) *Sleep 1980. 5th Eur. Congr. Sleep Res.* Karger, Basel, 1981: 16-22.
- Gilbert, P. *Depression: From Psychology to Brain State*. Lawrence Erlbaum Associates, London, 1984.
- Gillin, J. C. The sleep therapies of depression. *Progr. Neuropsychopharmacol. Biol. Psychiatry*, 1983, 7: 351-364.
- Gillin, J. C., Buchsbaum, M., Dupont, R. and Wu, J. Localized cerebral metabolism in man: effects of sleep and sleep deprivation. *Abstr. 10th European Congr. Sleep Res.*, Strasbourg, 1990.
- Gordijn, M., Beersma, D. G. M., Reinink, E., Gänshirt, G., Bouhuys, A. L. and van den Hoofdakker, R. H. Diurnal variation of mood, implications for depression research. In: C. N. Stefanis, A. D. Rabavilas and C. R. Soldatos (Eds) *Psychiatry: a World Perspective, Vol. 1*. Elsevier, Amsterdam, 1990: 489-493.
- Gorsuch, R. L. *Factor Analysis*. Lawrence Erlbaum Associates, Hillsdale NJ, 1983 (second edition).
- Gray, J. A. *The Psychology of Fear and Stress*. Cambridge University Press, Cambridge, 1987 (second edition).
- Hamilton, M. Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.*, 1967, 6: 278-296.
- Hamilton, M. The Hamilton rating scale for depression. In: N. Sartorius and T. A. Ban (Eds) *Assessment of Depression*. Springer-Verlag, Berlin, 1986: 143-152.
- Hockey, R. and Hamilton, P. The cognitive patterning of stress states. In: R. Hockey (Ed) *Stress and Fatigue in Human Performance*. Wiley, New York, 1983: 331-362.
- Horne, J. A. A review of the biological effects of total sleep deprivation in man. *Biol. Psychol.*, 1978, 7: 55-102.
- Horne, J. *Why We Sleep: The Functions of Sleep in Humans and Other Mammals*. Oxford University Press, Oxford, 1988.
- Horne, J. Dimensions to sleepiness. In: T. H. Monk (Ed.) *Sleep, Sleepiness and Performance*. Wiley, Chichester, 1991: 169-196.
- Isaacson, R. L. *The Limbic System*. Plenum Press, New York, 1982 (second edition).
- Joffe, R. T. and Swinson, R. P. Total sleep deprivation in patients with obsessive-compulsive disorder. *Acta Psychiatr. Scand.*, 1988, 77: 483-487.
- Johnson, L. C. Sleep deprivation and performance. In: W. B. Webb (Ed.) *Biological Rhythms, Sleep and Performance*. Wiley, New York, 1983: 111-141.
- Kahneman, D. *Attention and Effort*. Prentice Hall, Englewood Cliffs, NJ, 1973.
- Kiers, H. A. L. SCA: A Program for Simultaneous Component Analysis. IEC Programma, University of Groningen (PO Box 841, 9700 AV Groningen, The Netherlands), 1990.
- Kiers, H. A. L. and ten Berge, J. M. F. Alternating least squares algorithms for simultaneous components analysis with equal component weight matrices in two or more populations. *Psychometrika*, 1989, 54: 467-474.
- Kleitman, N. *Sleep and Wakefulness*. University of Chicago Press, Chicago, 1963 (second edition).
- Kuhs, H. and Tölle, R. Sleep deprivation therapy. *Biol. Psychiatry*, 1991, 29: 1129-1148.
- Lader, M. Anxiety and depression. In: A. Gale and J. A. Edwards (Eds) *Physiological Correlates of Human Behaviour, Vol. 3*. Academic Press, London, 1983: 155-167.
- Lader, M., Lang, R. A. and Wilson, G. D. *Patterns of Improvement in Depressed In-Patients*. Oxford University Press, Oxford, 1987.
- Letemendia, F. J. J., Prowse, A. and Southmayd, S. E. Diagnostic applications of sleep deprivation. *Can. J. Psychiatry*, 1986, 31: 731-736.
- Levenson, R. W. Personality research and psychophysiology: general considerations. *J. Res. Personality*, 1983, 17: 1-21.
- Lewis, A. Melancholia: a clinical survey of depressive states. *J. Ment. Sci.*, 1934, 80: 277-378.
- Luria, A. R. *The Working Brain*. Penguin Books, Middlesex, 1973.
- Mackay, C. J. The measurement of mood and psychophysiological activity using self-report techniques. In: I. Martin and P. H. Venables (Eds) *Techniques of Psychophysiology*. Wiley, New York, 1980: 501-562.
- Meddis, R. Cognitive dysfunction following loss of sleep. In: A. Burton (Ed.) *The Pathology and Psychology of Cognition*. Methuen, London, 1982: 225-252.
- Millsap, R. E. and Meredith, W. Component analysis in cross-sectional and longitudinal data. *Psychometrika*, 1988, 53: 123-134.
- Moruzzi, G. The functional significance of sleep with particular regard to the brain mechanisms underlying consciousness. In: J. C. Eccles (Ed.) *Brain and Conscious Experience*. Springer-Verlag, Berlin, 1966: 345-388.
- Murray, E. J. *Sleep, Dreams, and Arousal*. Meredith Publishing Company, New York, 1965.
- Neiss, R. Reconceptualizing arousal: psychobiological states in motor performance. *Psychol. Bull.*, 1988, 103: 345-366.
- Parry, B. L. and Wehr, T. A. Therapeutic effects of sleep

- deprivation in patients with premenstrual syndrome. *Am. J. Psychiatry*, 1987, 144: 808–810.
- Pflug, B. and Tölle, R. Therapie endogener Depressionen durch Schlafentzug. *Nervenarzt*, 1971, 42: 117–124.
- Pflug, B. The effect of sleep deprivation on depressed patients. *Acta Psychiatr. Scand.*, 1976, 53: 148–158.
- Post, R. M., Kotin, J. and Goodwin, F. K. Effects of sleep deprivation on mood and central amine metabolism in depressed patients. *Arch. Gen. Psychiatry*, 1976, 33: 627–632.
- Rechtschaffen, A., Bergmann, B. M., Everson, C. A., Kushida, C. A. and Gilliland, M. A. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep*, 1989, 12: 68–87.
- Reinink, E., Bouhuys, A. L., Wirz-Justice, A. and van den Hoofdakker, R. H. Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. *Psychiatr. Res.*, 1990a, 32: 113–124.
- Reinink, E., Bouhuys, A. L., Gordijn, M., van den Hoofdakker, R. H. and Beersma, D. G. M. Total sleep deprivation and diurnal variation in depression. In: C. N. Stefanis, A. D. Rabavilas and C. R. Soldatos (Eds) *Psychiatry: a World Perspective, Vol. 1*. Elsevier, Amsterdam, 1990b: 494–499.
- Roy-Byrne, P. P., Uhde, T. W. and Post, R. M. Antidepressant effects of one night's sleep deprivation: clinical and theoretical implications. In: R. M. Post and J. C. Ballenger (Eds) *Neurobiology of Mood Disorders*. Williams & Wilkins, Baltimore Md., 1984: 817–835.
- Roy-Byrne, P. P., Uhde, T. W. and Post, R. M. Effects of one night's sleep deprivation on mood and behavior in panic disorder. *Arch. Gen. Psychiatry*, 1986, 43: 895–899.
- Ruddöf, G. A. E. and Tölle, R. The course of the night with total deprivation as antidepressant therapy. *Waking and Sleeping*, 1978, 2: 83–91.
- Sanders, A. F. Towards a model of stress and human performance. *Acta Psychol.*, 1983, 53: 61–97.
- Southmayd, S. E. Diagnosing pseudodementia. *Hosp. Community Psychiatry*, 1989, 40: 753–754.
- Stuss, D. T. and Benson, D. F. *The Frontal Lobes*. Raven Press, New York, 1986.
- Thayer, R. E. Measurement of activation through self-report. *Psychol. Rep.*, 1967, 20: 663–678.
- Thayer, R. E. Activation states as assessed by verbal report and four psychophysiological variables. *Psychophysiology*, 1970, 7: 86–94.
- Thayer, R. E. Activation–deactivation adjective check list: Current overview and structural analysis. *Psychol. Rep.*, 1986, 58: 607–614.
- Thayer, R. E. *The Biopsychology of Mood and Arousal*. Oxford University Press, New York, 1989.
- Tölle, R. and Goetze, U. On the rhythm of depression symptomatology. *Psychopathology*, 1987, 20: 237–249.
- Valenstein, E. S. (Ed.) *The Psychosurgery Debate: Scientific, Legal and Ethical Perspectives*. Freeman, San Francisco, 1980.
- Van den Burg, W., Bouhuys, A. L., van den Hoofdakker, R. H. and Beersma, D. G. M. Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder. *J. Affect. Disord.*, 1990, 19: 109–117.
- Van den Burg, W. and van den Hoofdakker, R. H. Total sleep deprivation on endogenous depression. *Arch. Gen. Psychiatry*, 1975, 32: 1121–1125.
- Van den Hoofdakker, R. H. and Beersma, D. G. M. On the contribution of sleep wake physiology to the explanation and the treatment of depression. *Acta Psychiatr. Scand.*, 1988, 77: Suppl. 341, 53–71.
- Van den Hoofdakker, R. H., Bouhuys, A. L. and Beersma, D. G. M. The effects of sleep deprivation and sleep on depressive mood and subjective arousal. *Biol. Psychiatry*, 1989, 26: 733–736.
- Van den Hoofdakker, R. H., Bouhuys, A. L. and Beersma, D. G. M. Sleep deprivation. On the mechanisms of the antidepressant effects. *Abstr. 10th European Congr. Sleep Res.*, Strasbourg 1990.
- Von Zerssen, D. *Die Befindlichkeitsskala Manual*. Beltz Test Verlag, Weinheim, 1976.
- Von Zerssen, D. Clinical self-rating scales (CSRS) of the Munich Psychiatric Information System (PSYCHIS München). In: N. Sartorius and T. A. Ban (Eds) *Assessment of Depression*. Springer-Verlag, Berlin, 1986: 270–303.
- Wehr, T. A. Effects of wakefulness and sleep on depression and mania. In: J. Montplaisir and R. Godbout (Eds) *Sleep and Biological Rhythms. Basic Mechanisms and Applications to Psychiatry*. Oxford University Press, New York, 1990: 42–86.
- Wehr, T. A., Sack, D. A. and Rosenthal, N. E. Sleep reduction as a final common pathway in the genesis of mania. *Am. J. Psychiatry*, 1987, 144: 201–204.
- Wehr, T. A. and Wirz-Justice, A. Internal coincidence model for sleep deprivation and depression. In: W. P. Koella (Ed.) *Sleep 1980. 5th Eur. Congr. Sleep Res.* Karger, Basel, 1981: 26–33.
- Wilkinson, R. T. Sleep deprivation. In: O. G. Edholm and A. L. Bacharach (Eds) *Physiology of Survival*. Academic Press, London, 1965: 399–430.
- Willner, P. *Depression: A Psychobiological Synthesis*. Wiley, New York, 1985.
- Wu, J. C. and Bunney, W. E. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am. J. Psychiatry*, 1990, 147: 14–21.
- Zung, W. W. K., Wilson, W. P. and Dodson, W. E. Effect of depressive disorders on sleep EEG responses. *Arch. Gen. Psychiatry*, 1964, 10: 439–445.
- Zung, W. W. K. Effect of antidepressant drugs on sleeping and dreaming: III. On the depressed patient. *Biol. Psychiatry*, 1969, 1: 283–287.